39. A composition as claimed in claim 38 wherein the component products are separated from each other by a barrier.

40. A composition as claimed in claim 38 wherein the barrier is a physical barrier.

41. A composition as claimed in claim 40 wherein the physical barrier is a membrane provided between the component products.

42. A composition as claimed in claim 41 wherein the membrane is a coating of the components in microgranular or granular presentation.

43. A composition as claimed in claim 42 wherein the coating is provided on any one or all of the components within the formulation.

44. A composition as claimed in claim 38 wherein the barrier is a chemical barrier.

45. A product as claimed in any of claims 34 to 44 wherein at least a portion of the organic nitrate is present in a slow release form.

46. A product as claimed in any of claims 34 to 45 wherein the combination product comprises a capsule including the components.

47. A combination pharmaceutical product as claimed in any of claims 34 to 46 substantially as hereinbefore described with reference to the Examples.

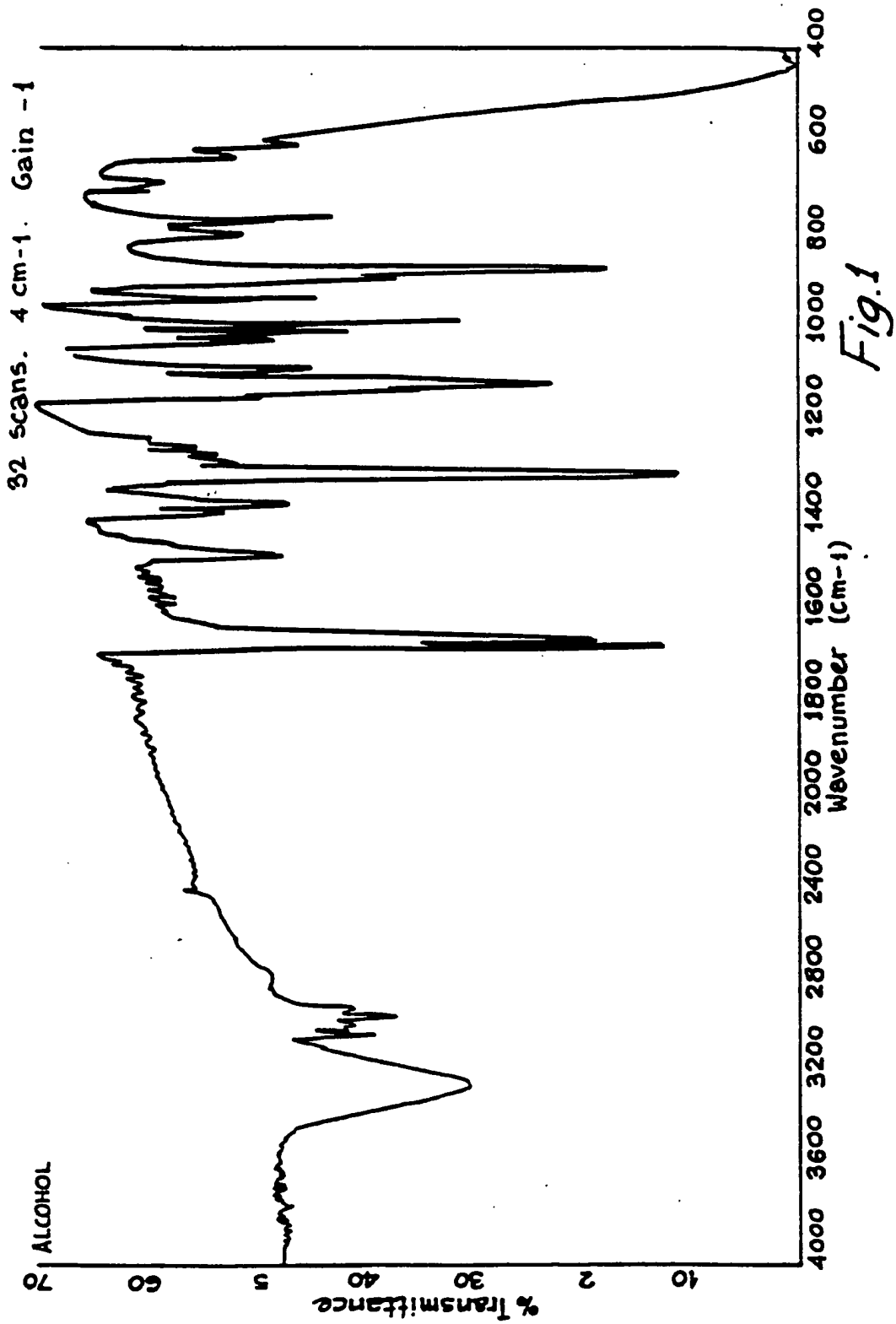
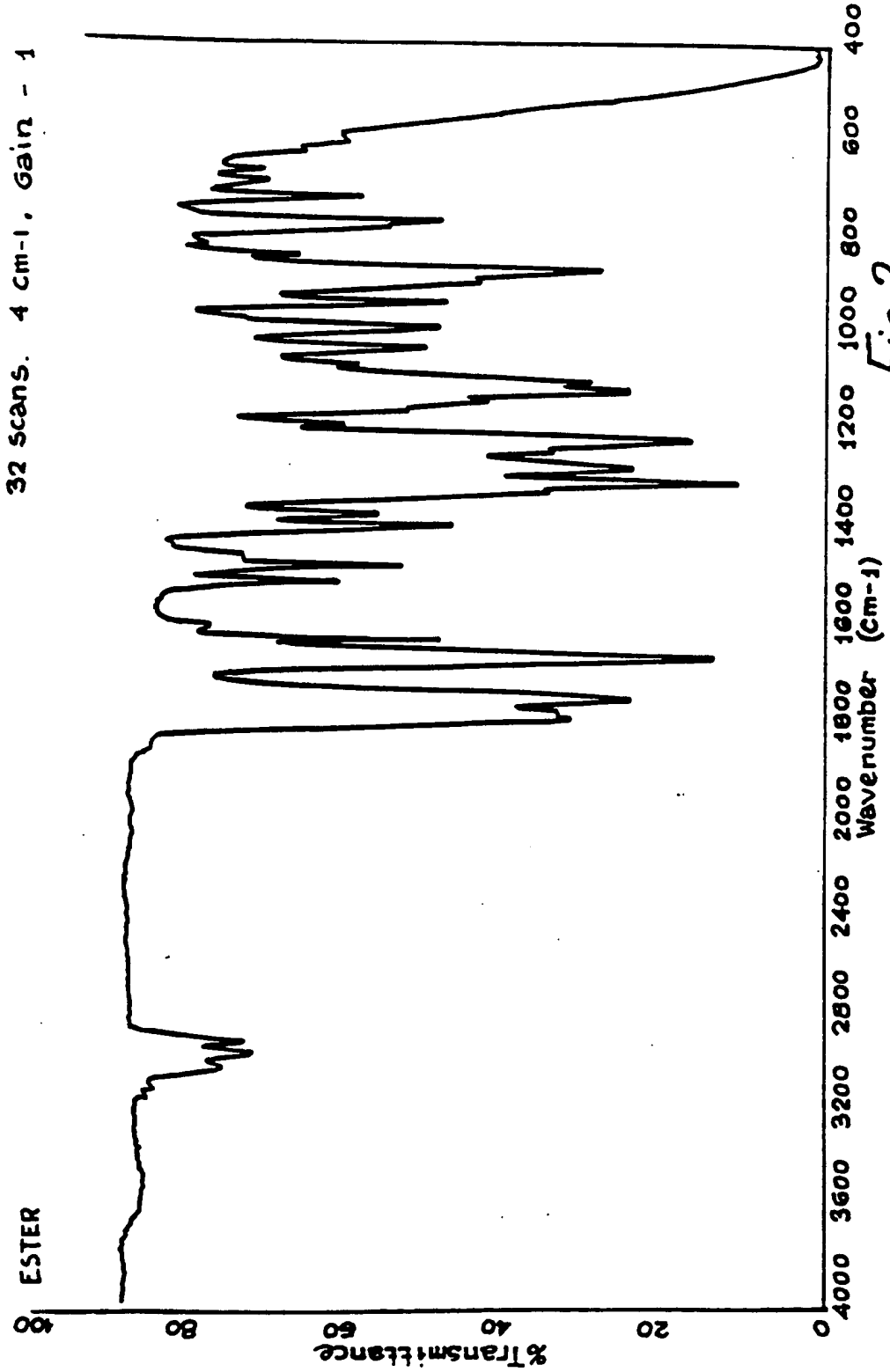

ALCOHOL
32 scans. 4 cm-1. Gain -1
% Transmittance
70 60 5 40 30 2 10
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
Wavenumber (cm-1)

Fig.1


ESTER
32 scans. 4 cm-1, Gain - 1
%Transmittance
100
80
60
40
20
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4000
3600
3200
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2400
2000
1800
1600
1400
1200
1000
800
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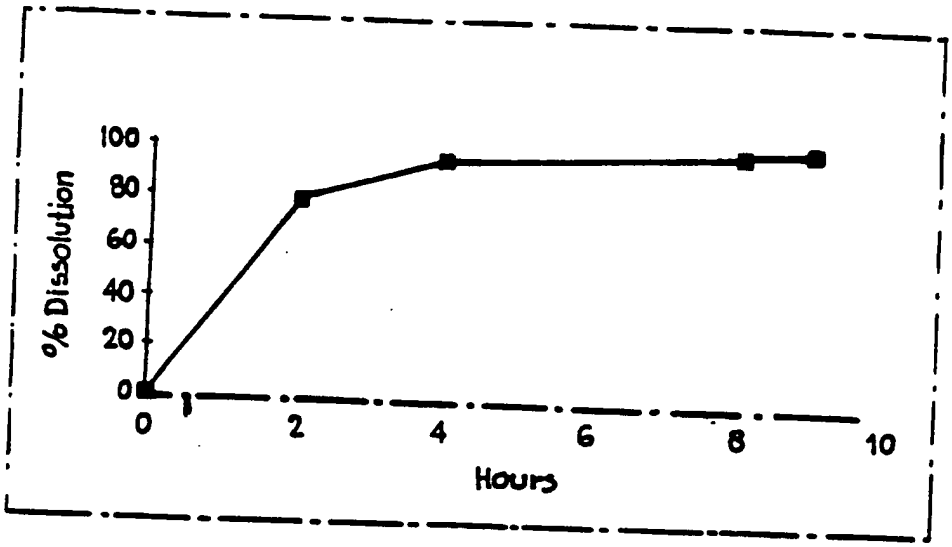
Wavenumber (cm-1)

Fig. 2


% Dissolution
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60
40
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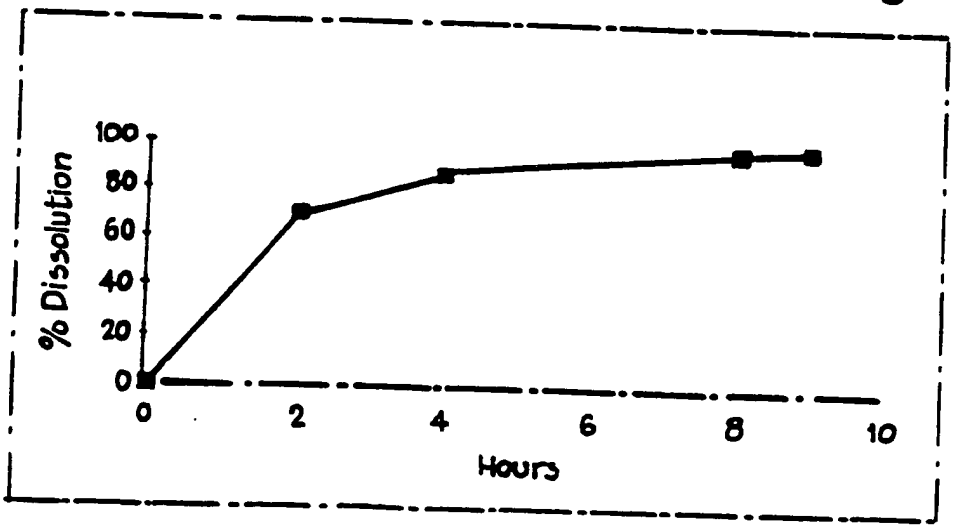
Hours

Fig.3


% Dissolution
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80
60
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6
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Hours

Fig.4

(19) Europäisches Patentamt
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(21) Application number: **95201369.6**

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(54) Combinations of an organic nitrate and a salicylate.

(57) A pharmaceutical composition comprises a single dose capsule for oral administration containing an organic nitrate, preferably isosorbide 5-mononitrate and acetylsalicylic acid. A coating on one or both of the organic nitrate or acetylsalicylic acid provides a barrier between them. Portion of the organic nitrate in the capsule is in a form for immediate release and portion is in a form for slow release.

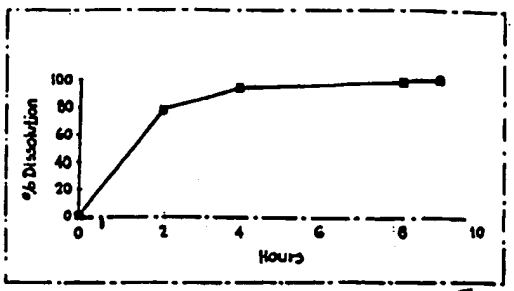


Fig. 1

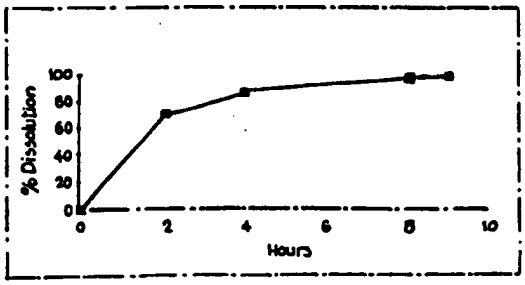


Fig. 2

EP 0 676 204 A1

The invention relates to pharmaceutical products.

The term "organic nitrates" as used in this specification refers to pharmacologically active organic nitrate compounds which r li v , or act as prophylactic against, angina pectoris.

Organic nitrates are dilators of arterial and venous smooth muscle. The dilation action on the venous system increases the venous capacity allowing pooling of venous blood. This in turn reduces the volume of blood returning to the heart thereby lessening the strains on the heart muscle by reducing the pressure in the heart chambers (ventricles). This, in turn, reduces the oxygen requirements of the heart muscle. The dilation action on the arterial system is achieved by increasing the volume of the arterial system with consequent lower resistance to blood flow. This, in turn, reduces the work that the heart is required to do. In the coronary arteries (heart) a transient widening of the arteries (vasodilation) increases blood circulation to the heart muscle thereby increasing oxygen availability to the heart muscle.

Patients with coronary artery narrowing may suffer from angina pectoris which is usually brought on by exercise, emotion or eating. The organic nitrates by virtue of their action described above relieve the symptoms of angina pectoris.

In more detail, organic nitrates act in two ways - indirectly or directly.

Indirectly : they are smooth muscle relaxants and thus dilate both arterial and venous blood vessels. At lower doses their action is mainly on the venous system resulting in a decreased right and left ventricular filling pressure. At lower doses, however, they have little effect on the systemic (arterial) filling pressure. At higher doses, the arterial effects are more marked and decreased systemic resistance is accompanied by a reduction in blood pressure (Flaherty et al 1976). The venodilating and arterial effects of nitrates relieve ischaemia (the cause of angina, pain) by reducing determinates of myocardial oxygen demand.

Directly: they relieve ischaemia by direct action on the coronary vasculature thereby increasing intercoronary collateral flow and reversal of coronary artery spasm.

One widely used organic nitrate is isosorbide mononitrate (ISMN) which is an active metabolite of Isosorbide dinitrate (ISDN). ISMN has a high bioavailability and has a comparatively long half life (4-5 hours). This it is very suitable for prophylactic angina therapy. this is particularly so when it is presented as a sustained release formulation.

According to the invention there is provided a pharmaceutical composition comprising a single dose capsule for oral administration containing an organic nitrate and acetylsalicylic acid, a physical barrier between the organic nitrate and acetylsalicylic acid, portion of the organic nitrate in the capsule being in a form for immediate release and portion being in a form for slow release.

The organic nitrate may be an isosorbide nitrate such as isosorbide 2-mononitrate or, most preferably isosorbide 5-mononitrate.

In a preferred arrangement, the weight ratio of organic nitrate to acetylsalicylic acid is from 2:1 to 1;5, most preferably approximately 1:1.

The barrier may be a physical barrier such as a membrane between the components. The membrane may be a coating of the components in microgranular or granular presentation. The coating may be on any or all of the components within the formulation.

The invention will be more clearly understood from the following description thereof given by way of example only.

A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

Aspirin (acetylsalicylic acid) has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agents. As such, it is a most useful drug.

In more recent years, however, it has been discovered that aspirin has a powerful antiplatelet effect. Platelets are microscopic particles within th blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin pr vents the sticking togeth r of platelets and thus h lps pr vent the occurrence of heart attack or its complications.

The weight ratio of the nitrate to Aspirin may be from 2:1 to 1:5, most preferably approximat ly 1:1.

The component products may be separated from each other by a coating of g latine or the like on one of the components, most preferably on the nitrate.

The effect of the pharmaceutical product of the invention is in the treatm nt of angina pectoris and in reducing the risk of d v loping myocardial infarction.

It is anticipated that, while the invention has been specifically described with reference to the combination of Isosorbide nitrate and Aspirin, it is expected that combination products of other known anti-angina agents may also be used.

Providing a nitrate and an anti platelet agent in a single dose pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin separately there is a risk that one or other will be forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

EXAMPLE 1

A capsule containing 80 mg of Aspirin, 15 mg of Isosorbide Mononitrate for immediate release and a slow release tablet containing 45 mg of Isosorbide Mononitrate was prepared.

A size 1 capsule was used. The ideal powder fill weight was in the region of 190 mg, containing 80 mg of Aspirin and 15 mg of Isosorbide Mononitrate. The formulation for the powder fill was :

A.	Aspirin	80 mg
	ISMN	15 mg
	Microcrystallinecellulose	90 mg
	Talc	4 mg
	Magnesium stearate	1 mg

A number of alternative formulations for a slow release tablet containing 45 mg of Isosorbide Mononitrate were made. The preferred formulation was :

B.	ISMN	45.0 mg
	Calcium H. Phosphate	30.0 mg
	Eudragit NE 40D	15.0 mg
	Magnesium Stearate	1.0 mg
	Water	q/s

The ISMN was blended with Calcium H. Phosphate and the resultant mix was granulated with Eudragit. The granules were sieved using a No. 10 sieve and dried at 40 °C for 6 to 8 hours. Magnesium stearate and talc were added and the mixture was blended prior to compression.

Dissolution tests of the capsule incorporating A and B yielded a good long term release profile which is plotted in Fig. 1.

EXAMPLE 2

Example 1 was repeated except that the granules of Example 1B were further blended with Eudragit RS/PO.

The results of dissolution tests are plotted in Fig. 2.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

Claims

1. A pharmaceutical composition comprising a single dose capsule for oral administration containing an organic nitrate and acetylsalicylic acid, a physical barrier between the organic nitrate and acetylsalicylic acid, portion of the organic nitrate in the capsul being in a form for immediate release and portion being in a form for slow r l ase.

2. A pharmaceutical composition as claimed in claim 1 wherein the physical barrier is in the form of a coating on one or more of the organic nitrate portion for slow release, the acetylsalicylic acid, and the

organic nitrate portion for immediate release.

3. A pharmaceutical composition as claimed in claim 1 or 2 wherein the organic nitrate for slow r lease is in th form of a tablet in the capsul .

4. A pharmaceutical composition as claimed in claim 1, 2 or 3 wherein the organic nitrate for immediate release is in a granular or microgranular form.

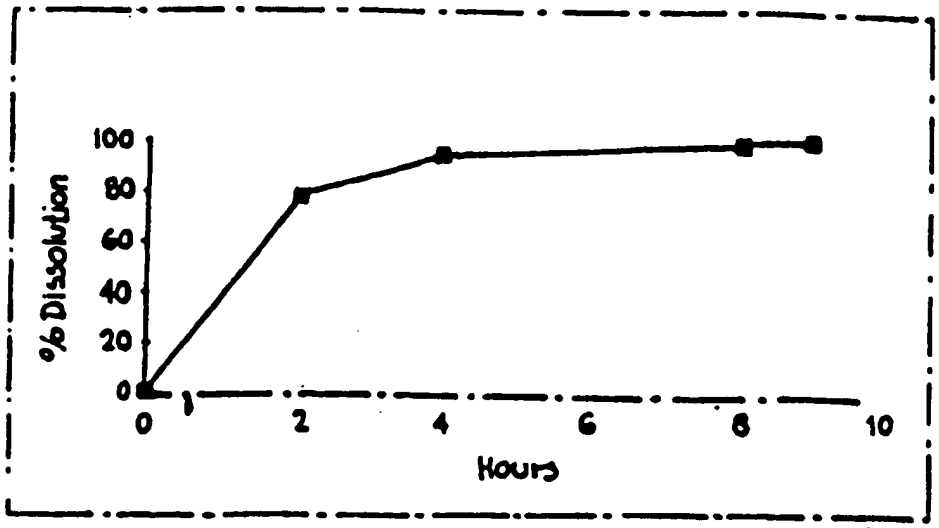
5. A pharmaceutical composition as claimed in any preceding claim wherein the organic nitrate is an isosorbide mononitrate.

6. A pharmaceutical composition as claimed in claim 5 wherein the organic nitrate is isosorbide 5-mononitrate.

7. A pharmaceutical composition as claimed in any preceding claim wherein the weight ratio of organic nitrate to acetylsalicylic acid is from 2:1 to 1:5.

8. A pharmaceutical composition as claimed in claim 7 wherein the weight ratio of organic nitrate to acetylsalicylic acid is approximately 1:1.

9. A pharmaceutical composition as claimed in claim 7 or 8 wherein the weight ratio or organic nitrate to acetylsalicylic acid is approximately 3:4.


% Dissolution
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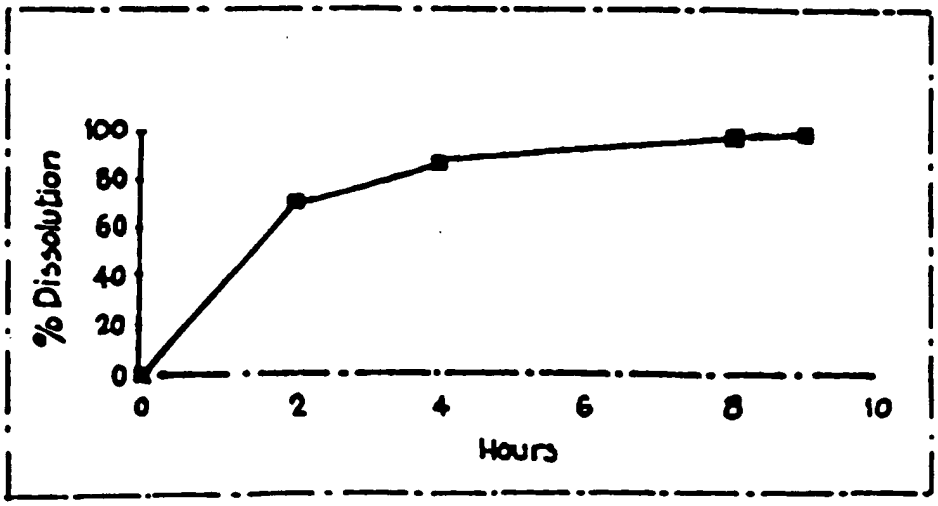
Hours

Fig. 1


% Dissolution
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Hours

Fig. 2

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 20 1369

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Y	FR-A-2 187 315 (PIERRE FABRE S.A.) * claims * ---	1-9	A61K31/60 A61K31/62 A61K31/625 A61K9/48 A61K9/50 //(A61K31/60, 31:21), (A61K31/60, 31:34)
Y	EUR. HEART J., vol.12 SUP.A, 1991 pages 2 - 4 C.R. CONTI 'Why use a nitrate in 1990?' * the whole document * ---	1-9	
Y	EUR. HEART J., vol.9 SUP. A, 1988 pages 45 - 49 R. DE CATERINA 'Mechanisms for the in vivo antiplatelet effects of isosorbide dinitrate.' * the whole document * ---	1-9	
Y	EUR. J. CLIN. PHARMACOL., vol.25, 1983 pages 779 - 782 E. REY 'Pharmacological interaction between nitroglycerin and aspirin after acute and chronic aspirin treatment of healthy subjects.' * the whole document * ---	1-9	TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61K
Y	J. CARDIOVASC. PHARMACOL., vol.5, no.5, 1983 pages 874 - 877 S. WEBER 'Influence of aspirin on the hemodynamic effects of sublingual nitroglycerin.' * the whole document * ---	1-9	
Y	EP-A-0 449 426 (INTERNATIONAL MEDICAL RESEARCH LIMITED) * the whole document * --- -/--	1-9	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26 July 1995	Orviz Diaz, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 20 1369

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Y	EP-A-0 396 425 (KV PHARMACEUTICAL COMPANY) * page 3, line 40 - page 4, line 26; claims 19-31; examples 7-10 * ---	1-9	
Y	EP-A-0 219 728 (BASF AG) * claims; examples 4,5 * ---	1-9	
P,Y	US-A-5 175 187 (S. BALIGADOO) * claims; example IV * ---	1-9	
Y	FR-A-2 368 272 (THERAMEX) * claims 1,3 * -----	1-9	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/000642 A2

(54) Title: DRUGS FOR CHRONIC PAINS

(57) Abstract: Nitro-oxyderivative compounds or salts thereof having the following general formula (I): A-$(B)_{b0}$-$(C)_{c0}$-NO_2 wherein: c0 is an integer and is 0 or 1, b0 is an integer and is 0 or 1, A = R-T_1-, wherein R is the radical of an analgesic drug for the chronic pain, in particular for the neuropathic pain; B is such that its precursor is selected from aminoacids, hydroxyacids, polyalcohols, compounds containing at least one acid function; C is a bivalent radical containing an aliphatic, heterocyclic or aromatic radical.

DRUGS FOR CHRONIC PAINS

* * * * *

The present invention relates to compounds having an improved efficacy in the reduction of the chronic pain, specifically the neuropathic pain.

For the description of the chronic pain, for simplicity, reference is made, from now on, to the neuropathic pain.

It is known that the neuropathic pain is a form of chronic pain originated from a damage or from a disease of the central or peripheral nervous system. The neuropathic pain comprises a series of painful symptomatologies, such for example the following: the diabetic neuropathic pain, the painful post-infarct syndrome, the pain caused by the chemotherapeutic treatment, or it can derive from an infection caused by viral agents, such for example herpes, for instance Herpes zoster, etc.

The neuropathic pain generally afflicts the patients for years since the therapies with conventional analgesic drugs are not effective. Furthermore it is a social problem since the neuropathic pain besides the physical trouble causes in the patients a serious psychological stress.

In the last twenty years the research on the pathogenesis of the neuropathic pain has achieved significant progress. Studies carried out on human and animal experimental models of neuropathic pain, have shown that the central nervous system reacts to the algogen stimuli with a series of biochemical and physiopathological responses. This capability of the nervous system to functionally and morphologically adapt itself with algogen stimuli, is known

as neuroplasticity and it has an essential role in inducing the onset or in maintaining the painful symptomatology.

Among the drugs used in the neuropathic pain treatment the carbamazepine has been widely used in clinical studies, and the results obtained have shown the efficacy of said drug in the treatment of trigeminal neuralgia, of the diabetic neuropathic pain and in the post-herpetic neuralgia. However the administration of this drug produces in patients marked side effects such as for example, somnolence, dizziness, ataxy, nausea and vomit, which limit the use thereof.

In these last years other drugs for the treatment of the neuropathic pain have been experimented. Among these, it is in particular mentioned gabapentin, which has a high analgesic efficacy for the neuropathic pain treatment, particularly the diabetic neuropathic pain and the post-herpetic pain. However the therapy with gabapentin causes side effects of central type such as somnolence, weariness, obesity, etc. (Martindale XXXth Ed. p.374).

The need was therefore felt to have available drugs having in the treatment of the chronic pain, in particular neuropathic pain, an improved pharmacotherapeutic profile and/or lower side effects.

It has now been surprisingly and unexpectedly found that this technical problem can be solved with the class of drugs which is described hereunder.

An object of the present invention are nitrooxyderivative compounds or salts thereof having th following general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = R-T_1-, wherein R is the radical of an antipain drug for the chronic pain, in particular for the neuropathic pain;

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -T_B-X_2-T_{BI}- wherein

T_B and T_{BI} are equal or different;

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B -T_B-X_2-T_{BI}- wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with

-$N(Z^I)(Z^{II})$, being:

Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible,

Z^I, Z^{II} equal to or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined is preferably selected from the following classes of compounds:

aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine,

glutathione or esters thereof, preferably ethyl or isopropyl ester;

hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;

aromatic and heterocyclic polyalcohols, selectd from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl alcohol, allopurinol;

compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein

when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

when b0 = 0 : T_c = (CO) when t = 0, T_c = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, T_{BI} = X = —O—;

Y has one of the following meanings:

Y_p:

$$-[C]_{nIX}-Y^3-[C]_{nIIX}-O- \qquad (III)$$

with R_{TIX} and R_{TIIX} on the respective carbons, and R_{TIX}· and R_{TIIX}· on the terminal carbons.

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H;

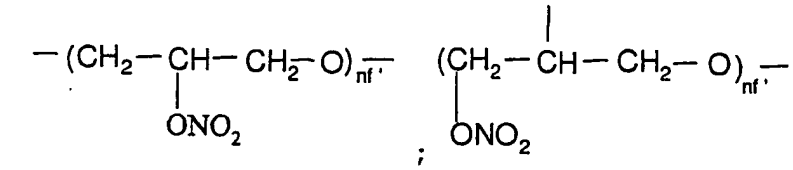
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms, containing from one to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

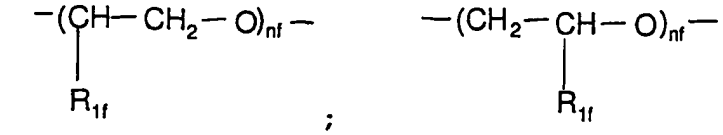
Y_0, selected from the following:

an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, having preferably from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

- 

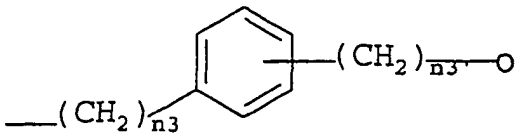
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 2 to 4;

Y_{AR}, selected from:

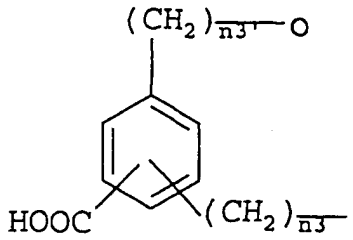
Y_{AR1}:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

Y_{AR2}:

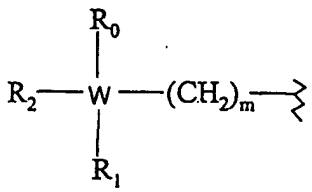


(VI)

wherein n3 and n3' have the above meaning.

The radical R in formula (I) is preferably that of chronic analgesic drugs, in particular of drugs for the neuropathic pain, and it can be selected from the conventional compounds used for these applications. Tricyclic antidepressive drugs and antiepileptic drugs can be mentioned.

Preferably R is the radical of an analgesic drug, having formula II:



(II)

wherein:

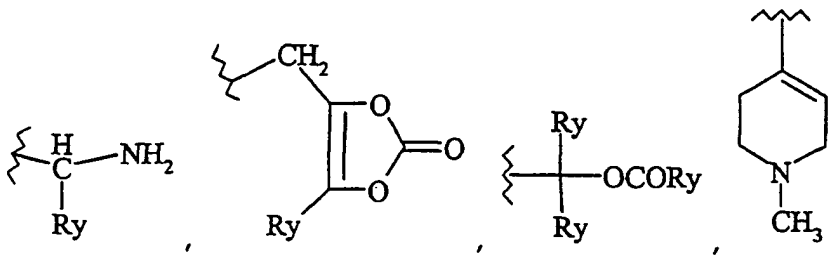
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

R_0 = H, $-(CH_2)_n-NHR_{1A}$, n being an integer from 0 to 2, wherein

R_{1A} = H, $-C(O)-R_{1H}$, $-C(O)O-R_{1H}$, wherein

R_{1H} is a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



(II-B) (II-C) (II-D) (II-E)

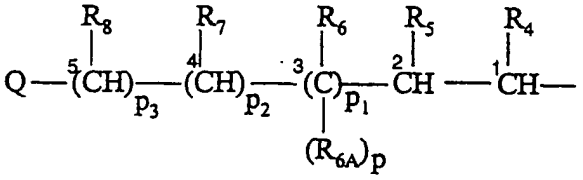
wherein Ry is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

R_1 = H, when W = N, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted benzyl;
- amidino group: $H_2N(C=NH)-$;
- the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between

the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

wherein:

p, p_1, p_2 are integers, equal to or different from each other and are 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1-C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1-C_6 alkyl,
- C_3-C_6 cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:
  - linear or branched C_1-C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
  - phenyl, optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_6, R_{6A}, R_7, R_8, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type between C_1 and C_2 is present, R_4 and R_5 are free valences

such as to form the double bond between C_1 and C_2; when the unsaturation is between C_3 and C_4, R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4; when the unsaturation is between C_4 and C_5, R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups: -OCH_3, -CF_3, nitro;

or Q can have one of the following meanings:

- C_3-C_6 cycloalkyl;
- linear or branched C_1-C_6 alkyl;
- guanidine ($H_2NC(=NH)NH$-);
- thioguanidine ($H_2NC(=S)NH$-);

in formula (II) R_2 with R_1 and with W = C taken together form a C_4-C_{10}, preferably C_6, saturated or unsaturated, preferably saturated, ring.

When in formula (II) W = C, m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_2 and R_1 with W as above defined form together the cyclohexane ring, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;

when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;

when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;

when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the thioguanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;

when in formula (II) W = C, m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

when in formula (II) W = C and has configuration (S), m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as (S)3-isobutylGABA;

when in formula (II) W = C, m = 1 and R_0 = R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;

when in formula (II) W = C, m = 2 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1